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09/755,233	01/08/2001	Padmanabhan P. Nair	NAIR-5	4931

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EXAMINER
UNGAR, SUSAN NMN

ART UNIT	PAPER NUMBER
1642	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/755,233	Nair
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 13, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *7-9 and 26-28* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *7-9 and 26-28* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Amendment and Election filed May 13, 2003 (Paper No. 11) in response to the Office Action of April 7, 2003 (Paper No. 9) is acknowledged and has been entered. Claims 7-9, 22 and 26-28 are pending in the application and Claim 22 has been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 7-9 and 26-28 are currently under prosecution.

2. Applicant's election of Group III, claims 7 and 26-28 in Paper No 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a). Further, upon review and reconsideration it is found that there is no additional burden of search for the search of claims 8 and 9, therefore, claims 8 and 9 are hereby rejoined to the invention of Group III.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

4. Claims 7-9 and 26-28 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by none of a specific utility, a well established utility or a substantial utility.

The disclosed utilities for the claimed immunocoprocytes include monitoring mucosal immunity (p. 13, line 6). In particular, it was discovered that an important

and advantageous feature of the non-invasively obtained colonocytes of the present invention is that these isolated colonic cells carry markers or transformations characteristic of the pathology of the GI tract and, therefore, they can serve as diagnostic and predictor indicators of the GI tract pathology (para bridging pages 12-13). Immunocoprocytes, IgA bearing colonocytes and Cfc receptor bearing colonocytes have distinct roles in immune surveillance of the GI tract and in maintaining systemic humoral immunity of the total organism. These cells perform vital functions including maintaining a balance in the colonization of the colon by microflora, recognizing soluble or particulate antigens of dietary or biological origin, they may act as antigen presenting cells to gut associated lymphoid tissue, they can be sentinels for detecting invasion of pathogens, their absence can signify a state of immunologic anergy of iatrogenic origin or congenital immunoglobulin deficiencies (para bridging pages 16-17). However, neither the specification nor any art of record teaches a specific utility for the immunocoprocytes, teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases for the claimed immunocoprocytes, thus the invention does not have specific utility. Disclosed utilities for the claimed immunocoproctyes include monitoring mucosal immunity, apparently for diagnostic or predictive purposes. However, neither the specification nor the art of record teaches what monitoring the mucosal immunity will impart, does not teach what GI pathology might be associated with alterations in immunocoprocyte expression of the claimed molecules or what alteration in the proliferation of immunocoprocytes might mean. Neither the expression of the claimed immunocoprocyte molecules nor the proliferation of the

claimed immunocoprocytes has not been correlated with any disease, thus, additional experimentation is required in order to determine a real world use for the claimed immunocoprocytes and the invention does not have substantial utility. Further disclosed utilities include performing vital functions including maintaining a balance in the colonization of the colon by microflora, recognizing soluble or particulate antigens of dietary or biological origin, acting as antigen presenting cells to gut associated lymphoid tissue, being sentinels for detecting invasion of pathogens, and finally, their absence can signify a state of immunologic anergy of iatrogenic origin or congenital immunoglobulin deficiencies. However, neither the specification nor the art of record teaches which immunocoprocytes are associated with any of these functions or what expression pattern of the claimed immunocoprocyte molecules is required to perform the suggested functions. Thus, additional experimentation is required in order to determine a real world use for the claimed immunocoprocytes and the invention does not have substantial utility.

The asserted utility of the claimed immunocoprocytes appears to be based on the hypothesis that since the colonic cells isolated from stools were discovered to be true representative of the anatomical and pathophysiological condition of the entire colon and since the mucosa of the GI tract is a major site for the elaboration of immunological defenses mediated by immunoglobulins, the newly discovered functionally distinctive group of cells that express an Fc receptor and immunoglobulin A and bind a chimeric immunoglobulin that is recognized by antibodies both to IgG and IgA (p. 13, lines 3-19) are useful for the disclosed utilities. Given that the asserted utility is based only on a hypothesis, it is clear that

additional work must be done in order to determine whether or not the hypothesis is related to fact, thus, once again, the invention does not have substantial utility. Although Kobayashi et al (J. Immunol., 1989, 143(8)2567-2574) has clearly discovered that colonocytes express a unique Fc binding site (and thus appear to be the claimed immunocoprocytes) (see abstract), Kobayashi et al did not determine how to use this information and specifically state that the function of the newly discovered Fc binding site awaits study (p. 2573, col 2). The authors hypothesized that the binding site might be involved in immunologic defense of the gut or might stimulate the secretion of intestinal mucus (p. 2573, col 2), but clearly additional work needed to be done to determine the function of the colonocytes expressing the unique Fc binding site. Thus, the instant invention does not have a well-established utility because the utility of the prior art colonocytes with Fc binding site, which appears to be the claimed immunocoprocyte expressing Cfc, is unknown. Finally, even if it were to be discovered that the isolated immunocoprocytes were related in some way to immunological disorders, the invention as originally filed would still not have substantial utility because there is no teaching of which immunological disorders the claimed immunocoprocytes are associated with. Further work must be clearly done in order to establish an association of the claimed immunocoprocytes with any disease and to determine whether or not they can be used to monitor mucosal immunity. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed immunocoprocytes. Because the claimed invention is not supported by a specific

utility, a well established utility, a substantial utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 7-9 and 26-28 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

7. Claims 7-9 and 26-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to immunocoprocytes expressing various molecules.

The specification teaches that since colonic cells isolated from stools were discovered to be true representative of the anatomical and pathophysiological conditions of the entire colon, among other utilities these cells also allow monitoring of mucosal immunity. It was discovered that an important and advantageous feature of the non-invasively obtained colonocytes/immunocoprocytes of the present

invention is that these isolated colonic cells carry markers or transformations characteristic of the pathology of the GI tract and, therefore, they can serve as diagnostic and predictor indicators of the GI tract pathology (para bridging pages 12-13). The mucosa of the GI tract is a major site for the elaboration of immunological defenses mediated by immunoglobulins. A functionally distinctive group of cells, immunocoprocytes can be identified and isolated from the exfoliated cells obtained by the methodologies of the present invention. They are unique in expressing a specific immunoglobulin designated as IgC which is recognized by antibodies to both IgG and IgA, immunocoprocytes are clonal, antigen-specific and characterized by the presence of Fc receptors and Immunoglobulin A (p. 13, lines 3-20). Immunocoprocytes can be obtained by FACS technique or by antibody-related isolation techniques (p. 14, lines `10-25). Table 2 shows some representative normal distribution of IgC, Cfc and IgA found in these cells. A deviation from the normal values would indicate a disease process involving the immune system (p. 16, lines 4-7). Immunocoprocytes have distinct roles in immune surveillance of the GI tract and in maintaining systemic humoral immunity and perform vital functions including maintaining a balance in the colonization of the colon by microflora, recognizing soluble or particulate antigens of dietary or biological origin, they may act as antigen presenting cells to gut associated lymphoid tissue, they can be sentinels for detecting invasion of pathogens, their absence can signify a state of immunologic anergy of iatrogenic origin or congenital immunoglobulin deficiencies (para bridging pages 16-17).

One cannot extrapolate the teaching of the specification to the enablement of the claims because there is no teaching in the specification as to what is meant by using the immunocoprocytes to "monitor of mucosal immunity". There is no information as to what to monitor for. The specification provides no teaching as to whether or not there is any change in any of the patterns of expression of the IgC, Cfc or IgA found in these cells that is in any way associated with alterations in mucosal immunity. There are no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict which or what alterations in patterns of expression of any of IgC, Cfc or IgA found in these cells is in any way associated with mucosal immunity or what pattern of expression could be used in an assay of these cells to monitor mucosal immunity with a reasonable expectation of success. Further, as drawn to the use of the immunocoprocytes as diagnostic and predictor indicators of GI tract pathology, again, the specification provides no teaching as to which GI tract pathologies the immunocoprocytes can be to either diagnose or predict. For example, the specification, in Table 2 describes the distribution of IgC, IgA and Cfc bearing colonic cells. Are all of these different types of cells useful for diagnosis or prediction of GI pathology? For which diseases can they be used? Can each cell type, that is those that bear IgA alone or Cfc alone or IcG alone, or any combination thereof be used to diagnose or predict all GI pathologies associated with the immune system? Can all of them or only some of them be used to diagnose or predict some diseases and if so, which ones? The same issues are drawn to each of the "vital functions recited above". There are no working examples which would provide

guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that any or which combination of these cell types can be used as suggested with a reasonable expectation of success. In particular, although Kobayashi et al, *Supra* has clearly discovered that colonocytes express a unique Fc binding site (and thus appear to be the claimed immunocoprocytes) (see abstract), Kobayashi et al did not determine how to use this information and specifically state that the function of the newly discovered Fc binding site awaits study (p. 2573, col 2). The authors hypothesized that the binding site might be involved in immunologic defense of the gut or might stimulate the secretion of intestinal mucus (p. 2573, col 2) but as of this date, an extensive search of the literature has not revealed a function for this Fc receptor. Finally it appears that, other than its ability to bind IgA and IgG, IgC is not at all characterized. The effect of IgC on the function of Cfc cannot be predicted so that even if a function were to be found for the colonocyte Fc receptor, the invention would still not be enabled for the reasons set forth above. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

As drawn to the "how to make" prong of 35 USC 112, first paragraph, although the specification teaches how to isolate the claimed immunocoprocytes, the specification does not teach how to make the claimed immunocoprocytes. There is no teaching of the concentration of each of IgC, IgA and CFc on immunocoprocytes. There is no teaching of the structures of either CFc or IgC. In particular, the specification teaches that the Fc receptor of immunocoprocytes has been designated as CFc receptor in order to distinguish the Fc receptor of immunocoprocytes from

other Fc receptors (p. 16, lines 1-5). This suggests that the only way to distinguish the CFc receptor from other Fc receptors is by its presence on colonocytes, now designated as immunocoprocytes. However, Kobayashi et al teach that the Fc receptor found on colonocytes is a "unique" Fc receptor. Is the instantly claimed CFc the same receptor? Does it bind the same Fc that is bound by the Kobayashi et al receptor, does it bind all Fc components of antibodies or does it, like the Fc of Kobayashi et al, only bind to the Fc of a particular antibody? The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art. Given the lack of information about the structures of the CFc and IgC molecules, one could not make the claimed immunocoprocytes with any reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 7-9 and 26-28 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dutta et al, (Gastroenterology, 1995, 108(4 SUPPL) A463.

Claims 27-28 recite immunocoprocytes being indicative of mucosal immunity and the numbers of isolated immunocoprocytes being indicative of level of gastrointestinal tract immune dysfunction. However, these limitation are viewed as a recitation of intended use and therefore are not given weight in comparing the claim with the prior art. Claims 25-26 read on the product claimed *per se*, which is immunocoprocytes isolated from fecal matter as claimed in claim 7, wherein the immunocoprocytes express IgC.

The claims are drawn to immunocoprocytes isolated from fecal matter, wherein the immunocoprocytes express IgC, IaG and CFc, CFc, wherein the immunocoprocytes are indicative of mucosal immunity, wherein when isolated, difference in the number of immunocoprocytes from a normal individual compared to the number from an individual suspected of immune dysfunction is indicative of level of gastrointestinal tract immune dysfunction.

Dutta et al teach colonocytes isolated from normal colon (see abstract). Although the reference does not teach immunocoprocytes expressing IgC, expressing IgA and Cfc, expressing Cfc, the method of the prior art comprises the same method steps as claimed in the instant invention, that is, isolating colonocytes from fecal matter from the same population of cells, normal cells, thus at least a subset of the isolated colonocytes will be the claimed immunocoprocytes and the immunocoprocytes are anticipated because isolation of the colonocytes will inherently lead to isolation of each type of immunocoprocyte claimed. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

11. Claims 7, 9, 27-28 are rejected under 35 U.S.C. § 103 as being unpatentable over Kobayashi et al (J. Immunol., 1989, 143(8)2566-2574) in view of Dutta et al, *Supra*.

The claims are drawn to immunocoprocytes isolated from fecal matter, wherein the immunocoprocytes express, CFc, wherein the immunocoprocytes are indicative of mucosal immunity, wherein when isolated, difference in the number of immunocoprocytes from a normal individual compared to the number from an individual suspected of immune dysfunction is indicative of level of gastrointestinal tract immune dysfunction.

Kobayashi et al teach binding of IgG Fc to normal colonic and small intestinal epithelium which was confirmed by ELISA with microtiter wells coated with a sonicated homogenate from human colonocytes. The Fc receptor is distinct from

known human Fc-. Gamma R by lack of recognition by mAb to those receptors and differences in affinity for various subclasses of human and murine IgG (see abstract). The reference further speculates that the unique IgG Fc binding site might be involved in immunologic defense of the gut, perhaps by mediating reactions between foreign Ag and the contents of goblet cells. The reference teaches as set forth above but does not teach immunocoprocytes isolated from fecal matter wherein the immunocoprocytes express Cfc.

Dutta et al teach as set forth above, that is isolated colonocytes which inherently include a subset of colonocytes which express Cfc. Dutta et al further teach that recent advances in cellular and molecular biology have led to development of reliable methods for isolation of viable colonic epithelial cells from fecal samples (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art, and one would have been motivated, at the time the invention was made to isolate viable colonocytes from fecal matter by the method of Dutta et al and to further isolate those colonocytes that express Cfc because Kobayashi et al specifically teach that the unique Fc binding site might be involved in immunologic defense of the gut, hypothesizing that the binding site mediates reactions between foreign Ag and the contents of goblet cells because isolated viable colonocytes expressing the unique Fc binding site could be used to further characterize the unique Fc receptor and determine whether or not it, in fact, is involved in immunologic defense of the gut.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
August 25, 2003